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Proc Natl Acad Sci U S A 1998 Oct 13;95(21):12580-5

Doxycycline control of prion protein transgene expression modulates prion disease in mice.

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Conversion of the cellular prion protein (PrPC) into the pathogenic isoform (PrPSc) is the fundamental event underlying transmission and pathogenesis of prion diseases. To control the expression of PrPC in transgenic (Tg) mice, we used a tetracycline controlled transactivator (tTA) driven by the PrP gene control elements and a tTA-responsive promoter linked to a PrP gene [Gossen, M. and Bujard, H. (1992) *Proc. Natl. Acad. Sci. USA* 89, 5547-5551]. Adult Tg mice showed no deleterious effects upon repression of PrPC expression (>90%) by oral doxycycline, but the mice developed progressive ataxia at approximately 50 days after inoculation with prions unless maintained on doxycycline. Although Tg mice on doxycycline accumulated low levels of PrPSc, they showed no neurologic dysfunction, indicating that low levels of PrPSc can be tolerated. Use of the tTA system to control PrP expression allowed production of Tg mice with high levels of PrP that otherwise cause many embryonic and neonatal deaths. Measurement of PrPSc clearance in Tg mice should be possible, facilitating the development of pharmacotherapeutics.

PMID: 9770528, UI: 98445413

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